Date of Approval: DEC 30 2005

FREEDOM OF INFORMATION SUMMARY

NADA 141-253

EQUIOXX Oral Paste

0.82 % firocoxib (w/w)

EQUIOXX Oral Paste is administered for up to 14 days for the control of pain and inflammation associated with osteoarthritis in horses.

Sponsored by:

Merial Limited
3239 Satellite Blvd.
Duluth, GA 30096

141-253

FOIS 1

Table of Contents

1. GENERAL INFORMATION:

a.	File Number:	NADA 141-253
b.	Sponsor:	Merial Ltd. 3239 Satellite Blvd., Bldg. 500 Duluth, GA 30096-4640 Drug Labeler Code: 050604
c.	Established Name:	firocoxib
d.	Proprietary Name:	EQUIOXX Oral Paste
e.	Dosage Form:	Oral Paste
f.	How Supplied:	EQUIOXX Oral Paste is available in packs of 20, 72 and 216 individually-boxed syringes.
g.	How Dispensed:	Rx
h.	Amount of Active Ingredients:	Each syringe contains 6.93 grams of 0.82% w/w firocoxib paste, sufficient to treat a 1250 lb horse.
i.	Route of Administration:	Oral
j.	Species/Class:	Equine
k.	Recommended Dosage:	0.045 mg/lb (0.1 mg/kg) body weight daily for up to 14 days
l.	Pharmacological Category:	Nonsteroidal anti-inflammatory
m.	Indications:	EQUIOXX Oral Paste is administered for up to 14 days for the control of pain and inflammation associated with osteoarthritis in horses.

2. *EFFECTIVENESS*

a. Dosage Characterization:

Two studies were conducted in support of the dosage characterization for the oral, once-daily 0.1 mg/kg dose of firocoxib (0.82% w/w) paste in horses.

(1) Study PR&D 0036901: A Dose Titration Study of ML-1,785,713 Oral Paste in Horses.

In this study, firocoxib oral paste was administered to a total of 18 horses (6 per treatment group) with lameness, at doses of 0.0625 (using 0.51% w/w formulation), 0.125 (using 1.03% w/w formulation), or 0.25 mg/kg (using 2.05% w/w formulation) once daily for seven days. Clinical observations were recorded at baseline (pre-treatment) and on Days 0, 2, and 6 (approximately 12 hours post-treatment). Primary clinical endpoints were peak vertical force (measured by force plate analysis) and lameness score. Plasma firocoxib concentrations were measured after the 1st, 3rd, and 7th doses at approximately 2, 12, and 24 hours post-dose. Clinical results indicated improvement relative to baseline at all three dose levels, with greater improvement at the 0.125 and 0.25 mg/kg doses. Dose linearity along with significant plasma drug accumulation was demonstrated among the three doses. This is consistent with the long half life (30-34 hours) of the firocoxib paste formulation in horses.

(2) Study PR&D 0065801/02: A Dose Titration Study of ML-1,785,713 Oral Paste in Horses.

In this study, firocoxib oral paste was administered to a total of 64 horses (16 per group) with lameness, at doses of 0.0, 0.05, 0.10, and 0.25 mg/kg once daily for seven days. Clinical observations were recorded at baseline (Day -1) and on Days 0, 2, and 6 (approximately 10 hours post-treatment). The primary clinical endpoints were the lameness score and peak vertical force. Plasma firocoxib concentrations were measured after the 1st, 3rd and 7th doses at approximately 10 and 24 hours post-dose. Clinical results indicated improvement in lameness and peak vertical force scores for both 0.1 and 0.25 mg/kg doses. Again, dose linearity along with significant plasma drug accumulation was observed among the doses.

The 0.1 mg/kg dose was selected for further study.

b. Substantial Evidence:

A multicenter field study was conducted at nine sites to demonstrate the effectiveness and safety of firocoxib administered for 14 days for the control of pain and inflammation associated with osteoarthritis in horses.

(1) Field Study (PR&D 000084201-07, 09-10)

Title: PR&D 00842: A Study to Assess the Efficacy, Safety and Acceptability of ML-1,785,713 Oral Paste in Horses for the Control of Pain and Inflammation Associated with Osteoarthritis Under Field Conditions

(a) Type of Study: Active-controlled, Masked, Randomized Field Studies

(b) Investigators:

Investigators	Locations
Dr. Michèle Doucet	Montreal, Québec, Canada
Dr. Faith Hughes	Ocala, FL
Dr. Craig Reinemeyer	Knoxville, TN
Dr. Charles MacAllister	Stillwater, OK
Dr. Roger Sifferman	Springfield, MO
Dr. Scott McClure	Ames, IA
Dr. Dean Hendrickson	Fort Collins, CO
Dr. Gary White	Sallisaw, OK
Dr. Alicia L. Bertone	Columbus, OH

(c) General Design:

(1) Purpose: The objective of this study was to demonstrate, under field use conditions, the effectiveness, safety and acceptability of firocoxib administered for 14 days for the control of pain and inflammation associated with osteoarthritis in horses.

(2) Test Animals: 253 client-owned horses of various breeds were enrolled. Effectiveness was evaluated in 240 horses and safety was evaluated in 252 horses. The horses ranged in age from 2 to 37 years and weighed from 595 to 1638 lbs. One hundred twenty-seven horses received firocoxib, and 126 received phenylbutazone.

(3) Control: Phenylbutazone 20% w/w oral paste for horses

(4) Diagnosis: Enrolled horses were diagnosed with osteoarthritis by radiographic evidence within the preceding 29 days. Navicular degeneration was also included with radiographic evidence of prominent bony change.

The most severely affected limb at the initial visit was assessed at all evaluations for the duration of the study.

(5) Dosage Form: Final market formulation of firocoxib (0.82% w/w) oral paste for horses

(6) Route of Administration: Oral

(7) Dosages Used: 0.045 mg/lb (0.1 mg/kg) body weight of firocoxib administered once daily; 1.0 g/500 lb body weight of phenylbutazone administered once daily

(8) Treatment Duration: 14 days

(9) Variables Measured: The Investigator conducted general health and physical examinations and lameness evaluations at the initial visit (V1: Day –4 to Day 1), at the study midpoint (V2: approximately Day 7), and at the study endpoint (V3: approximately Day 14). Serum chemistry was evaluated at V1, V2 and V3; hematology was evaluated at V1 and V3. The primary variable of effectiveness was clinical improvement in lameness as assessed by the Investigator at study endpoint (V3). Improvement was defined as one of the following:
   a. Reduction of at least 1 in overall lameness score, and/or
   b. Combined reduction of at least 3 in scores for joint swelling, range of motion, and pain on palpation/manipulation as assessed by the Investigator.

Overall lameness, pain on palpation or manipulation, range of motion and joint swelling were assessed at the three scheduled time points and scored as follows:

Overall Lameness Score (Based on American Association of Equine Practitioners (AAEP) Scoring System)

Grade 0: No lameness
Grade 1: Difficult to observe; not consistently apparent regardless of circumstances (e.g., carrying weight, circling, incline, hard surface, etc.)
Grade 2: Difficult to observe at a walk or trotting in straight line; consistently apparent under certain circumstances (e.g., carrying weight, circling, incline, hard surface, etc.)
Grade 3: Consistently observable at a trot under all circumstances
Grade 4: Obvious lameness, marked nodding, hitching or shortened stride
Grade 5: Minimal weight bearing in motion and/or at rest; inability to move

Joint circumference of the most severely affected joint and the contralateral joint were measured with a tape and assessed clinically. Joints that could not be measured (e.g., coffin joint) were assigned a missing score and were not analyzed.

Joint Swelling Score (Measurement as compared to joint of contralateral limb)
0 = No swelling (circumference not more than 3% larger than contralateral limb)
1 = Mild swelling (fibrosis or mild, palpable fluid distension; >3 to 10% larger than contralateral limb)
2 = Moderate swelling (obvious, palpable fluctuant fluid distension; >10 to 20% larger than contralateral limb)
3 = Severe swelling (pronounced, palpable firm fluid distension; >20% larger than contralateral limb)

Investigator Assigned Swelling Score (Clinical assessment)
0 = No swelling or not applicable
1 = Mild swelling (fibrosis or mild, palpable fluid distension)
2 = Moderate swelling (obvious, palpable fluctuant fluid distension)
3 = Severe swelling (pronounced, palpable firm fluid distension)

Range of Motion Assessment (Most severely affected limb)
0 = Normal
1 = Slightly reduced (< 25% reduction as compared to expected normal range of motion)
2 = Moderately reduced (25 – 50% reduction as compared to expected normal range of motion)
3 = Severely reduced (> 50 % reduction as compared to expected normal range of motion)

Pain on Manipulation or Palpation
0 = No response to firm pressure
1 = Mild pain (exhibits muscle tremors and/or slight avoidance movement in response to digital palpation or compression)
2 = Moderate pain (definite limb withdrawal in response to digital palpation or compression)
3 = Severe pain (marked withdrawal from attempted digital palpation or compression)

Owners subjectively scored improvement from the initial visit (V1) on approximately Days 7 and 14. Owners made daily health observations and assessed convenience of administration and acceptability of treatment on approximately Day 14.

Owner Assessment Criteria for Improvement
2 = Improved from initial visit
1 = No change from initial visit
0 = Worsened from initial visit

(d) Results: Two hundred fifty-three client-owned horses of various breeds were enrolled in the study. Two hundred forty horses were evaluated for effectiveness and 252 horses were evaluated for safety. Thirteen horses were dropped from the effectiveness evaluation for protocol non-compliance and 1 horse was dropped from the safety evaluation for protocol non-compliance. Of the 13 horses dropped from the effectiveness evaluation, 8 were in the active control treated horses and 5 were in the firocoxib treated horses. The 1 horse dropped from the safety evaluation was treated with the active control.

Treatment with 0.1 mg/kg firocoxib orally once daily resulted in overall clinical improvement that was comparable to the active control, phenylbutazone, at both study midpoint (Day 7) and endpoint (Day 14). Both treatment groups showed clinical improvement from the initial visit. The results are summarized in Table 1.

Table 1. Veterinarian Clinical and Non-Inferiority Evaluation

Group	Percentage of Horses with Overall Clinical Improvement in Lameness	
Treatment	Day 7 (Visit 2)	Day 14 (Visit 3)
Firocoxib (n=122)	82.0%	84.4%
Phenylbutazone (n=118)	83.9%	86.4%
Difference (Control-Test Article)	1.9%	2.0%
Is non-inferiority demonstrated? (Margin of difference is <15%)	Yes	Yes

Tables 2 and 3 summarize the percentage of horses that showed improvement from the initial visit for the secondary efficacy variables (lameness, pain on manipulation, joint swelling (observed), joint swelling (calculated), range of motion) at Visit 2 and Visit 3.

Table 2. Percentage of Horses Improved at Day 7 (± 3 days) Veterinarian Evaluation

	Percentage of Horses Showing Improvement @ Day 7	
Variable	Firocoxib (n=122)	Phenylbutazone (n=118)
Lameness	80.3%	83.1%
Pain on manipulation	59.2%	53.0%
Joint swelling (observed)	22.1%	15.2%
Joint swelling (calculated)	25.6%	11.2%
Range of motion	36.4%	24.6%

Table 3. Percentage of Horses Improved at V3 Veterinarian Evaluation

	Percentage of Horses Showing Improvement @ Day 14	
Variable	Firocoxib (n=122)	Phenylbutazone (n=118)
Lameness	83.6%	85.6%
Pain on manipulation	65.0%*	49.6%
Joint swelling (observed)	23.0%	25.4%
Joint swelling (calculated)	24.1%*	12.5%
Range of motion	40.5%*	30.5%

*$p \leq 0.05$

Based on owner evaluations at Day 7 and Day 14, improvement from initial visit was comparable for firocoxib and phenylbutazone. Table 4 summarizes the owner assessments of improvement. Both firocoxib and active control pastes were rated acceptable (97.6% and 95.2%, respectively) and convenient to administer (95.3% and 98.4%, respectively) by owners.

Table 4. Percentage of Horses Improved on Owner Assessment

	Percentage of Horses Showing Improvement	
Treatment	Day 7 (Visit 2)	Day 14 (Visit 3)
Firocoxib (n=122)	71.1%	73.8%
Phenylbutazone (n=118)	68.6%	74.4%

Mean hematology variables were within normal reference values for both treatment groups, although individual animals may have had values outside the reference range. There were no clinically significant changes noted. Within-treatment decreases from baseline in white blood cell (WBC) count and neutrophils were observed in the firocoxib-treated group. Within-treatment decreases in WBC count and neutrophils and increases in basophils were observed in the phenylbutazone-treated group.

In the firocoxib treated group, within-treatment increases in calcium were noted at V2, and decreases in glucose at V2 and V3. Mean calcium and glucose values were

within normal reference ranges, and no clinically significant effects were observed. In the phenylbutazone-treated group, within-treatment decreases in total globulin, glucose, and total protein, and increases in BUN and albumin/globulin ratio were noted at V2 and V3. Mean glucose, total protein, and BUN values were within normal reference ranges, though there were some horses with values outside reference ranges. No clinically significant changes were observed. The total globulin mean in the firocoxib treated group was slightly outside the reference range. No clinically significant changes were observed. The albumin/globulin ratio mean values were slightly below normal reference range. No clinically significant effects were observed.

(e) Statistical Analysis: The primary effectiveness variable was subjective clinical improvement at study end (V3) as assessed by the Investigator. Comparison of treatments for incidence of clinical improvement was performed as a non-inferiority comparison with a one-sided lower 95% confidence limit. Improvement at study midpoint (V2) was also analyzed. Improvement was defined as (1) Reduction of at least one grade in lameness score, and/or (2) Combined reduction of at least 3 in scores for pain on manipulation/palpation, joint swelling (calculated and observed), and range of motion. Improvement was assigned a value of "0" if not improved and "1" if improved.

Secondary efficacy variables included clinical improvement, improvement in lameness score, pain on manipulation score, range of motion score and joint swelling scores as reported by the Investigator at V2, and Owner assessment of improvement on Days 7 and 14.

(f) Conclusions: In field studies, firocoxib was shown to be safe and effective when administered at 0.1 mg/kg orally once daily for the control of pain and inflammation associated with osteoarthritis in horses. Owners found firocoxib oral paste both convenient to administer (95.3%) and acceptable (97.6%) to their horses.

(g) Adverse Reactions: Adverse reactions were reported in both treatment groups during the studies. Adverse events are summarized in Table 5.

Table 5. Adverse Reactions Seen During U.S. Field Studies

Adverse Reactions	EQUIOXX n=127	Active Control n=125
Abdominal pain	0	1
Diarrhea	2	0
Excitation	1	0
Lethargy	0	1
Loose manure	1	0
Polydipsia	0	1
Urticaria	0	1

*Horses may have experienced more than one adverse reaction during the study.

3. TARGET ANIMAL SAFETY

Title: PR&D 0016801: A Study to Evaluate the Safety of Firocoxib (0.82% w/w) Administered to Horses in an Oral Paste Formulation at 1, 3, and 5X the Recommended Dose for Thirty Days

(1) Type of Study: GLP Laboratory Study

(2) Study Location: Merial-Missouri Research Center, Fulton, MO

(3) General Design:

(a) Purpose: To determine the safety of firocoxib administered to horses orally once daily at 1, 3, and 5X the recommended dose of 0.1 mg/kg for 30 days.

(b) Test Animals: Thirty-six healthy horses (12 male castrates and 24 females, ranging in weight from 741 to 1228 lbs, and in age from 2 to 5 years) were randomly assigned to 6 treatment groups.

(c) Control: Control horses were sham-dosed.

(d) Dosage Form: Paste containing 0.82% firocoxib w/w in the final market formulation.

(e) Route of administration: Oral

(f) Dosage: See Table 1.

Table 1. Treatment Groups, PR&D 0016801

Treatment Groups	Dose, mg/kg	Number and Sex of Animals
1	0	2 male castrates and 4 females
2	0.1 mg/kg (1X) on Days 0-29, Necropsy on Day 30	2 male castrates and 4 females
3	0.3 mg/kg (3X) on Days 0-29, Necropsy on Day 30	2 male castrates and 4 females
4	0.5 mg/kg (5X) on Days 0-29, Necropsy on Day 30	2 male castrates and 4 females
5	0.3 mg/kg (3X) on Days 0-29, held for 60 days after last treatment, no necropsy	2 male castrates and 4 females
6	0.5 mg/kg (5X) on Days 0-29, held for 60 days after last treatment, no necropsy	2 male castrates and 4 females

(g) Duration of Treatment: 30 days

(h) Variables measured: Physical examination, general and post-dosing observations, body weight, clinical chemistry, coagulation (APTT, Prothrombin time, and Thrombin Clotting Time), hematology, buccal mucosal bleeding time, plasma levels of firocoxib, urinalysis, and gross and microscopic evaluation.

(i) Statistical Analysis Methodology: A repeated measures analysis of covariance was used to analyze continuous variables.

(4) Results: None of the horses died in this study or showed serious clinical signs of toxicity; however, clinically significant abnormalities (oral lesions in the 3X and 5X groups) were seen on physical examination and at necropsy. Oral lesions consisted of ulcers and erosions of the tongue, lips and gums.

Clinical pathology abnormalities were seen in the 5X group (lowered RBC, HCT and hemoglobin; lowered total protein, albumin, and globulin) but were most likely associated with parasitism.

(5) Conclusions: Administration of the recommended dose of 0.1 mg firocoxib/kg body weight as an oral paste for 30 days was not associated with any adverse effects.

Title: PR&D 0083001: A Study to Evaluate the Safety of Firocoxib Administered to Horses in an Oral Paste Formulation at 1, 3, and 5X the Recommended Dose for Forty-two Days.

(1) Type of Study: GLP Laboratory Study

(2) Study Location: Merial-Missouri Research Center, Fulton, MO

(3) General Design:

(a) Purpose: To determine the safety of firocoxib administered to horses orally once daily at 1, 3, and 5X the recommended dose of 0.1 mg/kg for 42 days.

(b) Test Animals: Thirty-two healthy horses (16 male castrates and 16 females, ranging in weight from 713 to 1230 lbs, and in age from 2 to 5 years) were randomly assigned to 4 treatment groups.

(c) Control: Control horses were sham-dosed.

(d) Dosage Form: Paste containing 0.82% firocoxib w/w in the final market formulation.

(e) Route of administration: Oral

(f) Dosage: See Table 2.

Table 2. Treatment Groups, PR&D 0083001

Treatment Groups	Dose, mg/kg	Number and Sex of Animals
1	0	4 male castrates and 4 females
2	0.1 mg/kg (1X)	4 male castrates and 4 females
3	0.3 mg/kg (3X)	4 male castrates and 4 females
4	0.5 mg/kg (5X)	4 male castrates and 4 females

(g) Duration of Treatment: 42 days

(h) Variables measured: Physical examination, general and post-dosing observations, body weight, clinical chemistry, coagulation (APTT, Prothrombin time, and Thrombin Clotting Time), hematology, buccal mucosal bleeding time, plasma levels of firocoxib, urinalysis, gastric endoscopy, and gross and microscopic evaluation.

(i) Statistical Analysis Methodology: A repeated measures analysis of covariance was used to analyze continuous variables.

(4) Results: All horses survived to the end of the study. On physical examination pre-study, horses in all study groups had a similar incidence of oral ulcers present on the inside of the lips, at the commissure of the mouth and on the buccal (cheek) mucosa. On Days 14 and 28 of the study, the control horses that had oral ulcers pre-study no longer had oral ulcers, yet ulcers persisted in all of the treated groups. In addition, the incidence and severity of oral ulcers increased in all of the treated groups (1X, 3X, 5X). On examination at the study end, there was an increase in the incidence of oral cavity (lip, gingiva, tongue) ulcers in the 3X and 5X horses. Microscopic findings for these groups paralleled the gross findings. In addition, statistically the incidence of lip ulcers observed grossly ($p=0.0756$) and microscopically ($p=0.0345$) increased as the dose increased.

Clinical chemistry and coagulation abnormalities were seen in several horses in the 5X group. One 5X male horse developed a mildly elevated BUN and creatinine over the course of the study. This horse also had a concurrent prolonged bleeding time. At the study end this horse had a dilated pelvis of the right kidney. Another 5X male had a similar mild increase in creatinine during the study but did not have any abnormal findings at the end of the study. After two weeks of treatment, one female in the 5X group had a prolonged bleeding time. At the study end she was also found to have bilateral tubulointerstitial nephropathy and bilateral papillary necrosis.

Tubulointerstitial nephropathy occurred in one 3X female, two 3X male horses, and the 5X female horse with the prolonged bleeding time discussed above. The nephropathy had segmented cortical and medullary zones of dilated tubules accompanied by interstitial inflammation and edema. Papillary necrosis was present in one 1X male horse and the 5X female horse described above. Despite the gross and microscopic renal lesions, all of the horses were clinically healthy and had normal hematology, clinical chemistry and urinalysis values.

Analysis of plasma levels of firocoxib indicated that the drug was absorbed and systemically available at all doses. Plasma concentrations increased with dose, and were approximately dose proportional for the 1X and 3X dose groups. There was minimal or no increase in plasma concentration observed between the 3X and 5X, suggesting the presence of a saturable absorption process that can limit the magnitude of the absorbed (over)dose.

(5) Conclusions: Firocoxib administered once daily at the recommended dose of 0.1 mg/kg body weight in a 0.82% oral paste formulation for 42 days causes oral ulceration and is associated with delayed healing of pre-existing oral ulcers. One horse treated at the recommended dose for 42 days had renal papillary necrosis.

Title: PR&D 0030701: A Safety Study to Evaluate the Toxicity of Firocoxib Oral Paste to Horses for Ninety-two Days

(1) Type of Study: GLP Laboratory Study

(2) Study Location: Merial-Missouri Research Center, Fulton, MO

(3) General Design:

(a) Purpose: To evaluate the safety of firocoxib administered to horses orally once daily at 2.5X, 7.5X and 12.5X of the recommended dose of 0.1 mg firocoxib/kg body weight for 92 days.

(b) Test animals: Thirty horses (10 male castrates, 5 males and 15 females), ranging in age from 1 to 3 years, and weighing 690 to 1043 lbs were randomly assigned to 5 treatment groups. Group 5 was a recovery group to evaluate the reversibility of toxicity following approximately 92 days of treatment plus an additional 55-57 days without treatment.

(c) Control: Control horses were sham dosed.

(d) Dosage Form: Paste containing 2.05% firocoxib w/w in a formulation similar to, but not identical to, final market formulation.

(e) Route of administration: Oral

(f) Dosage: See Table 3.

Table 3. Treatment Groups, PR&D 0030701

Treatment Group	Dose, (mg/kg) 2.05 % w/w	Number and Sex of Animals	Duration of Treatment
1	0	3 Female (F) 1 Male (M) 2 Male Castrates (MC)	92 days
2	0.25 mg/kg (2.5X)	3 F, 1 M, 2 MC	92 days
3	0.75 mg/kg (7.5X)	3 F, 1 M, 2 MC	92 days
4	1.25 mg/kg (12.5X)	3 F, 1 M, 2 MC	92 days
5	1.25 mg/kg (12.5X)	3 F, 1 M, 2 MC	92 days (+55-57 days off dose)

(g) Treatment duration: 92 days

(h) Variables measured: Body weight, physical examination, post-dosing observations, plasma firocoxib levels, clinical chemistry, coagulation, hematology, urinalysis, oral and gastric endoscopy, and gross and microscopic evaluation.

(i) Statistical Analysis Methodology: A repeated measures analysis of covariance was used to analyze continuous variables.

(4) Results: There were no treatment-related deaths during the study; however, two horses died during the study. Ulcers of the lips, gingiva and tongue were seen in all treated groups (2.5X, 7.5X and 12.5X). The incidence of lip ulcers observed microscopically (inflammation, p=0.0044; erosions, p=0.0006; ulcers, p=0.0229, Cochran-Armitage trend test) increased as the dose increased. The incidence of tongue ulcers observed grossly (p=0.0018, Cochran-Armitage trend test) and microscopically (inflammation, p=0.0109; foreign body, p=0.0198; ulcers, p=0.0109, Cochran-Armitage trend test) increased as the dose increased.

Erosions of the skin of the mandible were seen grossly in all firocoxib-treated groups. The incidence of skin erosions observed microscopically (chronic active inflammation, p=0.0554, Cochran-Armitage trend test) increased as the dose increased.

Gross and microscopic lesions of the kidneys consistent with tubulointerstitial nephropathy were seen in all treated groups. Papillary necrosis was seen in the 2.5X and 12.5X groups. The incidence of kidney abnormalities observed grossly

(p=0.0149, Cochran-Armitage trend test) and microscopically (p=0.0189, Cochran-Armitage trend test) increased as the dose increased.

Three 12.5X animals also had elevated GGT, SDH, ALT and AST values. Two of these three horses had nephropathy but no other abnormalities at the study end. Three horses in the 2.5X group and three horses in the 7.5X group had single erosions or ulcers in the glandular stomach; however, glandular stomach ulcers were not seen in the placebo or the 12.5X groups. One 2.5X horse had elevated urine GGT and urine protein on Day 28 of the study and at necropsy this horse had renal lesions consistent with NSAID toxicity and renal hemorrhage. Group 5 showed that the oral ulcers were partially reversible after 55-57 days off treatment, but the renal lesions were not.

Plasma firocoxib concentrations were approximately dose linear between the 2.5X and 7.5X dose groups, and somewhat lower than expected in the 12.5X group. There was no evidence of drug accumulation or significantly decreased drug bioavailability occurring at any time point between days 14, 28, 63, and 89/90.

(5) Conclusions: Firocoxib administered once daily at 2.5X, 7.5X and 12.5X the recommended dose of 0.1 mg/kg using a 2.05% w/w paste formulation for 92 days confirmed the toxicity of firocoxib in horses. Treatment for approximately three months was associated with dose dependent increases in incidence and severity of oral ulcers, skin ulcers of the mandible, and nephropathy. Horses dosed at 12.5X for 92 days, then left untreated for an additional 55-57 days, showed partial to complete recovery from the oral and skin lesions, but renal lesions persisted.

4. HUMAN SAFETY

This drug is intended for use in horses, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human food safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the label as follows: "Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans."

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that EQUIOXX Oral Paste when used under the labeled conditions of use is safe and effective for the control of pain and inflammation

associated with osteoarthritis in horses.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to diagnose and treat pain and inflammation associated with osteoarthritis in horses.

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. New studies were conducted to support the effectiveness and safety of EQUIOXX Oral Paste in horses for the control of pain and inflammation associated with osteoarthritis in horses.

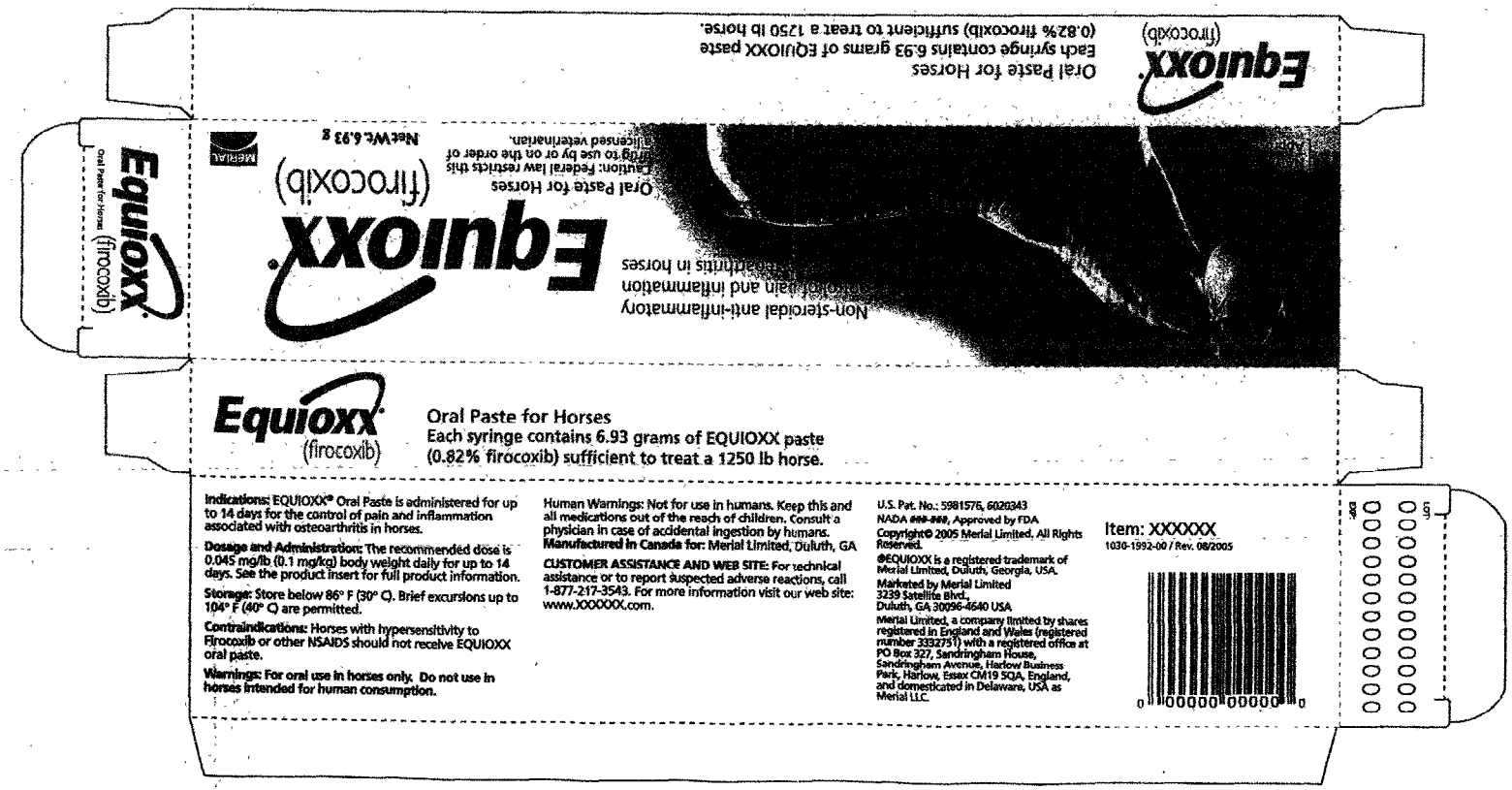
EQUIOXX Oral Paste is under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
5,981,576	October 9, 2016
6,020,343	October 9, 2016

6. ATTACHMENTS:

Veterinary Package Insert
Client Information Sheet
Syringe Label
Carton Label

12.460



Equioxx (firocoxib)

Oral Paste for Horses

Each syringe contains 6.93 grams of EQUIOXX paste (0.82% firocoxib) sufficient to treat a 1250 lb horse.

Non-steroidal anti-inflammatory for control of pain and inflammation associated with osteoarthritis in horses

Oral Paste for Horses

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Net Wt. 6.93 g

MERIAL

Equioxx (firocoxib)

Oral Paste for Horses

Each syringe contains 6.93 grams of EQUIOXX paste (0.82% firocoxib) sufficient to treat a 1250 lb horse.

Indications: EQUIOXX® Oral Paste is administered for up to 14 days for the control of pain and inflammation associated with osteoarthritis in horses.

Dosage and Administration: The recommended dose is 0.045 mg/lb (0.1 mg/kg) body weight daily for up to 14 days. See the product insert for full product information.

Storage: Store below 86° F (30° C). Brief excursions up to 104° F (40° C) are permitted.

Contraindications: Horses with hypersensitivity to Firocoxib or other NSAIDS should not receive EQUIOXX oral paste.

Warnings: For oral use in horses only. Do not use in horses intended for human consumption.

Human Warnings: Not for use in humans. Keep this and all medications out of the reach of children. Consult a physician in case of accidental ingestion by humans.

Manufactured in Canada for: Merial Limited, Duluth, GA

CUSTOMER ASSISTANCE AND WEB SITE: For technical assistance or to report suspected adverse reactions, call 1-877-217-3543. For more information visit our web site: www.XXXXXX.com.

U.S. Pat. No.: 5981576, 6020343

NADA ###-###, Approved by FDA

®EQUIOXX is a registered trademark of Merial Limited, Duluth, Georgia, USA.

Marketed by Merial Limited
3239 Satellite Blvd.,
Duluth, GA 30096-4640 USA

Merial Limited, a company limited by shares registered in England and Wales (registered number 3332751) with a registered office at PO Box 327, Sandringham House, Sandringham Avenue, Harlow Business Park, Harlow, Essex CM19 5QA, England, and domesticated in Delaware, USA as Merial LLC.

Item: XXXXXX

1030-1992-00 / Rev. 08/2005

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Fold (4)
6.0625"
Front

10.8125"

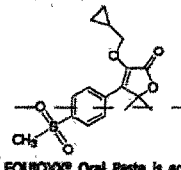
Equioxx®

Oral Paste for Horses (firocoxib)

Non-steroidal anti-inflammatory drug for oral use in horses only.

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description: EQUIOXX® (firocoxib) belongs to the coxib class of non-narcotic, non-steroidal anti-inflammatory drugs. Firocoxib is a white crystalline compound described chemically as 3-(cyclopropylmethoxy)-4-(4-(methylsulfonyl)phenyl)-5,5-dimethylfuranone. The empirical formula is $C_{17}H_{20}O_5S$, and the molecular weight is 336.4. The structural formula is shown below:



Indications: EQUIOXX® Oral Paste is administered for up to 14 days for the control of pain and inflammation associated with osteoarthritis in horses.

Dosage and Administration: Always provide the Client Information Sheet with the prescription. The recommended dosage of EQUIOXX® (firocoxib) for oral administration in horses is 0.045 mg/lb (0.1 mg/kg) of body weight once daily for up to 14 days. In target animal safety studies, toxicity was seen at the recommended dose when the duration of treatment exceeded 30 days.

Each marking on the syringe will treat 250 pounds of body weight, and each notch corresponds to approximately a 90 lb weight increment. To deliver the correct dose, round the horse's body weight up to the nearest 50 pound increment (if the body weight is an exact 50 pound increment, do not round up). Unlock the knurled ring on the syringe plunger by rotating it ¼ turn. Slide the knurled ring along the plunger shaft so that the side nearest the barrel is at the appropriate 50 lb weight notch. Rotate the plunger ring ¼ turn to lock it in place and ensure it is locked.

EQUIOXX® may be given with or without food.

Contraindications: Horses with hypersensitivity to firocoxib or other NSAIDs should not receive EQUIOXX® Oral Paste.

Warnings: For oral use in horses only. Do not use in horses intended for human consumption.

Human Warnings: Not for use in humans. Keep this and all medications out of the reach of children. Consult a physician in case of accidental ingestion by humans.

Animal Safety: Clients should be advised to observe for signs of potential drug toxicity and be given a Client Information Sheet with each prescription.

For technical assistance or to report suspected adverse events, call 1-877-217-3543.

Precautions: Horses should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests should be conducted to establish hematological and serum biochemical baseline data before and periodically during administration of any NSAID.

Clients should be advised to observe for signs of potential drug toxicity and be given a Client Information Sheet with each prescription. See Information for Owner or Person Treating Horse section of this package insert.

Treatment with EQUIOXX® should be terminated if signs such as inappetance, colic, abnormal feces, or lethargy are observed.

Fold (3)

As a class, cyclooxygenase inhibitory NSAIDs may be associated with renal and gastrointestinal toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Patients at greatest risk for adverse events are those that are dehydrated, on diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached or avoided. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since many NSAIDs possess the potential to produce gastrointestinal ulcerations, concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided or closely monitored. The concomitant use of protein bound drugs with EQUIOXX® Oral Paste has not been studied in horses. The influence of concomitant drugs that may inhibit the metabolism of EQUIOXX® Oral Paste has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

Fold (2)

The safe use of EQUIOXX® Oral Paste in horses less than one year in age, horses used for breeding, or in pregnant or lactating mares has not been evaluated.

Consider appropriate washout times when switching from one NSAID to another NSAID or corticosteroid.

Fold (1)

Adverse Reactions: In controlled field studies, 127 horses (ages 3 to 37 years) were evaluated for safety when given EQUIOXX® Oral Paste at a dose of 0.045 mg/lb (0.1 mg/kg) orally once daily for up to 14 days. The following adverse reactions were observed. Horses may have experienced more than one of the observed adverse reactions during the study.

Adverse Reactions Seen in U.S. Field Studies

Adverse Reactions	EQUIOXX® (n=127	Active Control (n=125
Abdominal pain	0	1
Diarrhea	2	0
Excitation	1	0
Lethargy	0	1
Loose stool	1	0
Polydipsia	0	1
Urticaria	0	1

EQUIOXX® (firocoxib) Oral Paste was safely used concomitantly with other therapies, including vaccines, anthelmintics, and antibiotics, during the field studies.

Information for Owner or Person Treating Horse: You should give a Client Information Sheet to the person treating the horse and advise them of the potential for adverse reactions and the clinical signs associated with NSAID intolerance. Adverse reactions may include erosions and ulcers of the gums, tongue, lips and face, weight loss, colic, diarrhea, or icterus. Serious adverse reactions associated with this drug class can occur without warning and, in rare situations, result in death. Clients should be advised to discontinue NSAID therapy and contact their veterinarian immediately if any of these signs of intolerance are observed. The majority of patients with drug-related adverse reactions recover when the signs are recognized, drug administration is stopped, and veterinary care is initiated.

Fold (4)
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Front

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Clinical Pharmacokinetics / Pharmacodynamics:
Pharmacokinetics: When administered as a 0.045 mg/lb (0.1 mg/kg) dose in oral paste to adult horses with normal access to roughage, feed, and water, the absolute bioavailability of firocoxib from EQUIOXX® paste is approximately 79%. Following oral administration, drug peak concentration (Cmax) of 0.08 mcg/mL can be reached at 4 hours (Tmax) post-dosing. However, in some animals, up to 12 hours may be needed before significant plasma concentrations are observed. Little drug amount distributes into blood cells. The major metabolism mechanism of firocoxib in the horse is decyclopropylmethylation followed by glucuronidation of that metabolite. Based upon radiolabel studies, the majority of label is eliminated in the urine as the decyclopropylmethylated metabolite. Despite a high rate of plasma protein binding (98%), firocoxib exhibits a large volume of distribution (mean Vd(ss) = 1882 mL/kg). The terminal elimination half-life (T½) in plasma averages 30-40 hours after IV or oral paste dosing. Therefore, drug accumulation occurs with repeated dose administrations and steady state concentrations are achieved beyond 6-8 daily oral doses in the horse. Dose linearity exists from 1X-2X of 0.1 mg/kg/day.

Mode of action: EQUIOXX® (firocoxib) is a cyclooxygenase-inhibiting (coxib) class, non-narcotic, non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic activity in animal models.

Effectiveness: Two hundred fifty-three client-owned horses of various breeds, ranging in age from 2 to 37 years and weighing from 595 to 1638 lbs, were randomly administered EQUIOXX® or an active control drug in multi-center field studies. Two hundred forty horses were evaluated for effectiveness and 252 horses were evaluated for safety. Horses were assessed for lameness, pain on manipulation, range of motion, joint swelling, and overall clinical improvement in a non-inferiority evaluation of EQUIOXX® compared to an active control. At study's end, 84.4% of horses treated with EQUIOXX® were judged improved on veterinarians' clinical assessment, and 73.8% were also rated improved by owners. Horses treated with EQUIOXX® showed improvement in veterinarian-assessed lameness, pain on manipulation, range of motion, and joint swelling that was comparable to the active control.

Acceptability: EQUIOXX® Oral Paste was rated both convenient to administer (96.3%) and acceptable to the horse (97.5%) by owners in the multi-center field study.

Animal Safety: In a target animal safety study, firocoxib was administered orally to healthy adult horses (two male castrates and four females per group) at 0, 0.1, 0.3 and 0.5 mg firocoxib/kg body weight (1, 3 and 5X the recommended dose) for 30 days. Administration of firocoxib at 0.3 and 0.5 mg/kg body weight was associated with an increased incidence of oral ulcers as compared to the control group but no oral ulcers were noted with 0.1 mg/kg. There were no other drug-related adverse findings in this study.

In another target animal safety study, firocoxib was administered orally to healthy adult horses (four males or male castrates and four females per group) at 0, 0.1, 0.3 and 0.5 mg firocoxib/kg body weight (1, 3 and 5X the recommended dose) for 42 days. Administration of firocoxib at 0.1, 0.3 and 0.5 mg/kg body weight was associated with delayed healing of pre-existing oral (lip, tongue, gingival) ulcers. In addition, the incidence of oral ulcers was higher in all treated groups as compared to the control group.

Clinical chemistry and coagulation abnormalities were seen in several horses in the 0.5 mg/kg (5X) group. One 5X male horse developed a mildly elevated BUN and creatinine over the course of the study, prolonged buccal mucosal bleeding time (BMBT), and a dilated pelvis of the right kidney. Another 5X male had a similar mild increase in creatinine during the study but did not have any gross abnormal findings. One female in the 5X group had a prolonged BMBT, bilateral tubulointerstitial nephropathy and bilateral papillary necrosis.

Tubulointerstitial nephropathy occurred in one 3X female, two 3X male horses, and the 5X female horse discussed above with the prolonged BMBT. Papillary necrosis was present in one 1X male horse and the 5X female horse discussed above. Despite the gross and microscopic renal lesions, all of the horses were clinically healthy and had normal hematology, clinical chemistry and urinalysis values.

In another target animal safety study, firocoxib was administered orally to healthy adult horses (three females, two male castrates and one male per group) at 0, 0.25 mg/kg, 0.75 mg/kg and 1.25 mg/kg (2.5, 7.5 and 12.5X the recommended dose of 0.1 mg/kg) for 92 days. An additional group of three females, two male castrates and one male per group, was dosed at 1.25 mg/kg for 92 days but was monitored until Days 147-149. There were treatment-related adverse events in all treated groups. These consisted of ulcers of the lips, gingiva and tongue and erosions of the skin of the mandible and head. Gross and microscopic lesions of the kidneys consistent with tubulointerstitial nephropathy were seen in all treated groups. Papillary necrosis was seen in the 2.5X and 12.5X groups. In addition, several 12.5X horses had elevated liver enzymes (GGT, SDH, AST and ALT). One 2.5X horse had increased urine GGT and urine protein levels which was due to renal hemorrhage and nephropathy. Gastric ulcers of the margo plicatus and glandular area were more prevalent in the 2.5X and 7.5X groups, but not seen in the 12.5X group. The group of horses that were monitored until Days 147-149 showed partial to full recovery from oral and skin ulcers, but no recovery from tubulointerstitial nephropathy.

Storage Information: Store below 86° F (30° C). Brief excursions up to 104° F (40° C) are permitted.

How Supplied: EQUIOXX® is available in packs of 20, 72 and 216 individually-boxed syringes. Each syringe contains 6.93 grams of EQUIOXX® paste, sufficient to treat a 1250 lb. horse.

For technical assistance or to report suspected adverse reactions, call 1-877-217-3543.

NADA #### ####, Approved by FDA

U.S. Pat. No.: 5981576, 6025343

EQUIOXX is a registered trademark of Merial Limited, Duluth, Georgia, USA.

1650-2913-00 Rev. 8/2005

MERIAL

FRONT

5"

Equioxx® (firocoxib)

Oral Paste for Horses

Non-steroidal anti-inflammatory drug

Information for Horse Owners

For technical assistance or to report suspected adverse reactions, call 1-877-217-3543.

NADA ###-###, Approved by FDA

U.S. Pat. No.: 5981576, 6020343

®EQUIOXX is a registered trademark of Merial Limited, Duluth, Georgia, USA.

1051-2011-00 Rev. 8/2005

MERIAL

EQUIOXX® Oral Paste is administered for up to 14 days for the control of pain and inflammation associated with osteoarthritis in horses.

This summary contains important information about EQUIOXX®. You should read this information before you start giving your horse EQUIOXX® paste and review it each time your prescription is refilled. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or you want to know more about EQUIOXX®.

What is EQUIOXX®?

EQUIOXX® is a veterinary prescription non-steroidal anti-inflammatory drug (NSAID) of the coxib class used to control pain and inflammation associated with osteoarthritis in horses. Osteoarthritis (OA) is a painful condition caused by progressive "wear and tear" of cartilage and other parts of the joints that may result in the following changes or signs in your horse:

- Limping or lameness.
- Decreased activity or exercise (reluctance to stand, walk, trot or run, or difficulty in performing these activities).
- Stiffness or decreased movement of joints.

How to give EQUIOXX® to your horse.

EQUIOXX® should be given according to your veterinarian's instructions. Do not change the way you give EQUIOXX® to your horse without first speaking with your veterinarian. Do not exceed 14 days of treatment.

The recommended dosage of EQUIOXX® (firocoxib) for oral administration in horses is 0.045 mg/lb (0.1 mg/kg) of body weight once daily for up to 14 days. Each marking on the syringe will treat 250 pounds of body weight, and each notch corresponds to approximately a 50 lb weight increment. To deliver the correct dose, round the horse's body weight up to the nearest 50 pound increment (if the body weight is an exact 50 pound increment, do not round up). Unlock the knurled ring on the syringe plunger by rotating it 1/4 turn. Slide the knurled ring along the plunger shaft so that the side nearest the barrel is at the appropriate 50 lb weight notch. Rotate the plunger ring 1/4 turn to lock it in place and ensure it is locked.

EQUIOXX® may be given with or without food.

What kind of results can I expect when my horse is on EQUIOXX® for OA?

While EQUIOXX® is not a cure for osteoarthritis, it can control the pain and inflammation associated with OA and can improve your horse's mobility.

- Response varies from horse to horse, but improvement can be quite dramatic.
- Improvement can be seen in just a few hours in most horses.

Which horses should not receive EQUIOXX®?

Your horse should not be given EQUIOXX® if he/she:

- Has an allergic reaction to firocoxib, the active ingredient in EQUIOXX®.
- Has previously had an allergic reaction (such as hives, facial or lower limb swelling, or red or itchy skin) to aspirin or other NSAIDs.
- Is presently taking aspirin, phenylbutazone, flunixin meglumine, diclofenac, ketoprofen, or other NSAIDs or corticosteroids.
- The safety of EQUIOXX® has not been determined in horses less than one year of age or in breeding horses, pregnant or lactating mares.

7"

BACK

5"

EQUIOXX® paste should only be given orally to horses.

- EQUIOXX® is not for use in horses intended for human food consumption.
- People should not take EQUIOXX®. Keep EQUIOXX® and all medications out of the reach of children. Consult a physician in case of accidental ingestion by humans.

What to tell/ask your veterinarian before giving EQUIOXX®.

Talk to your veterinarian about:

- The signs of OA you have observed in your horse, such as limping or stiffness.
- If any tests, such as X-rays, will be done before EQUIOXX® is prescribed.
- How often your horse may need to be examined by your veterinarian.
- The risks and benefits of using EQUIOXX®.

Tell your veterinarian if your horse has ever had the following medical problems:

- Any side effects from taking EQUIOXX® or other NSAIDs, such as aspirin or phenylbutazone.
- Any kidney disease.
- Any liver disease.
- Any gastrointestinal ulcers.

Tell your veterinarian about:

- Other medical problems or allergies that your horse has now, or has had in the past.
- All medicines that you are giving or plan to give to your horse, including those you can get without a prescription and any dietary supplements.

Tell your veterinarian if you plan to breed your horse, or if your mare is pregnant or nursing a foal.

What are the possible side effects that may occur in my horse during EQUIOXX® therapy?

EQUIOXX®, like other NSAIDS, may cause some side effects. Serious side effects associated with NSAID therapy in horses can occur with or without warning. The most common side effects associated with EQUIOXX® therapy involve the tongue, lips and skin of the mouth and face (erosions and ulcers of the mucosa and skin) and the kidney. Gastrointestinal, kidney and liver problems have also been reported with other NSAIDs. Look for the following side effects that may indicate your horse is having a problem with EQUIOXX® or may have another medical problem:

- Sores or ulcers on the tongue and inside of mouth.
- Sores, scabs, redness, or rubbing of the facial skin, particularly around the mouth.
- Change in eating or drinking habits (frequency or amount consumed).
- Change in urination habits (frequency or color).
- Yellowing of gums, skin, or whites of the eyes (jaundice).
- Unexpected weight loss.
- Change in behavior (such as increased or decreased activity level).

It is important to stop therapy and contact your veterinarian if you think your horse has a medical problem or side effect while taking EQUIOXX® paste. If you have additional questions about possible side effects, talk with your veterinarian or call 1-877-217-3543.

Can EQUIOXX® be given with other medications?

EQUIOXX® should not be given with other NSAIDs (for example, aspirin, phenylbutazone, diclofenac, ketoprofen or flunixin) or systemic corticosteroids (for example, prednisone, cortisone, dexamethasone, or triamcinolone).

Tell your veterinarian about all medications that you have given your horse in the past, and any medications you are planning to give with EQUIOXX® paste. This should include other medicines that you can get without a prescription or any dietary supplements. Your veterinarian may want to check that all of your horse's medicines can be given together.

What do I do in case my horse receives more than the prescribed amount of EQUIOXX®?

- Consult your veterinarian if your horse receives more than the prescribed amount of EQUIOXX®.

What else should I know about EQUIOXX®?

- This sheet provides a summary of information about EQUIOXX® paste and general information about NSAIDs. If you have any questions or concerns about EQUIOXX® or osteoarthritis pain, talk with your veterinarian.
- As with all prescribed medicines, EQUIOXX® paste should only be given to the horse for which it is prescribed. It should be given to your horse only for the condition for which it is prescribed, at the labeled dose and duration.
- It is important to periodically discuss your horse's response to EQUIOXX® paste. Your veterinarian will determine if your horse is responding as expected and if your horse should continue receiving EQUIOXX® paste.

Proof # 1
Client: Patheon Whitby
Item #: 356211-04A RevA
M.S.F.#: 312742
Size: 3.9375" X 1.75"
Colours: Black (UVF), pattern varnish
Proof for colour separation / film positive for type clarity.
Date: Aug. 26/04